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EXAMINER

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1634

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27

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/269,573

Applicant(s)

HAYASHIZAKI, YOSHIHIDE

Examiner

BJ Forman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 June 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-25 and 27-30 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-25 and 27-30 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

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DETAILED ACTION

1. This action is in response to papers filed 21 June 2002 in Paper No. 26 in which an Appeal Brief was submitted. The Appeal Brief, arguments and pending claims have been thoroughly reviewed. The previous rejections in the Office Action of Paper No. 2 dated 22 October 2001 are withdrawn in view of new grounds for rejection. The arguments have been considered and are discussed as they apply to the new grounds for rejection.

Currently claims 1-25 and 27-33 are under prosecution.

Specification

2. The amendments filed 18 January 2000 in Paper No. 9 and 12 March 2001 in Paper No. 17 are objected to under 35 U.S.C. 132 because they introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: "all of the sequence of a full-length gene". The specification, as originally filed, teaches that the material to be fixed on a substrate may be DNA fragments, RNA fragments, PNA fragments, full length cDNA, EST and genome DNA including plasmids, phages, PAC, BAC and YAC (page 4, last paragraph and page 5, third full paragraph). Additionally, Claim 22, as originally filed recites "all of cDNA sequence of a full length gene". However, neither the specification nor the claims as filed provide support for the recitation "all of the sequence of a full-length gene" as introduced in the amendment of Paper No. 9. Therefore, the amendment constitutes new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

35 U.S.C. 112: First paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-22, 32 and 33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To the extent that the claimed composition/or methods are not described in the instant disclosure, claims 1-22, 32 and 33 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

The recitation "all of a sequence of a full-length gene" is added to the independent claims 1 and 9 which were amended in Paper No. 9, filed 18 January 2000 and new claims 32 and 33 which were added in Paper No. 17, filed 12 March 2001. However, the specification fails to define or provide any disclosure to support such claim recitation. The specification, as originally filed, teaches that the material to be fixed on a substrate may be DNA fragments, RNA fragments, PNA fragments, full length cDNA, EST and genome DNA including plasmids,

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phages, PAC, BAC and YAC (page 4, last paragraph and page 5, third full paragraph).

Additionally, Claim 22, as originally filed recites "all of cDNA sequence of a full length gene".

The specification, as filed, does not provide support for the recitation "all of the sequence of a full-length gene" as introduced in the amendments of Paper No. 9 and Paper No. 17.

Therefore, the amendment constitutes new matter.

MPEP 2163.06 notes "IF NEW MATTER IS ADDED TO THE CLAIMS, THE EXAMINER SHOULD REJECT THE CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH - WRITTEN DESCRIPTION REQUIREMENT. *IN RE RASMUSSEN*, 650 F.2D 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application." MPEP 2163.06 further notes "WHEN AN AMENDMENT IS FILED IN REPLY TO AN OBJECTION OR REJECTION BASED ON 35 U.S.C. 112, FIRST PARAGRAPH, A STUDY OF THE ENTIRE APPLICATION IS OFTEN NECESSARY TO DETERMINE WHETHER OR NOT "NEW MATTER" IS INVOLVED. *APPLICANT SHOULD THEREFORE SPECIFICALLY POINT OUT THE SUPPORT FOR ANY AMENDMENTS MADE TO THE DISCLOSURE*" (emphasis added).

35 U.S.C. 112: Second paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-22 and 28-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-8 and 19-21 are indefinite in Claim 1 (A) for the recitation "which fragments are selected from the group consisting of one or more nucleic acid fragments and one or more PNA fragments and have all of a sequence of a full-length gene" because it is unclear how the "fragments" relate to the full length gene. It is unclear whether the "fragments" together, in combination, have "all of a sequence of a full-length gene" or whether each of the fragments

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have "all of a sequence of a full-length gene". Given the later meaning, it is contradictory that "fragments" encompass a full-length gene because fragments are inherently incomplete, not full-length. For purposes of examination, the claim is interpreted as meaning the combination of fragments has all of a sequence of a full-length gene.

b. Claims 1-8 and 19-21 are indefinite in Claim 1 (B) for the recitation "binding a labeled protein" because it is unclear to what the labeled protein is binding. It is suggested that Claim 1 be amended to clarify.

c. Claims 1-8 and 19-21 are indefinite in Claim 1 (B) for the recitation "between the hybridized fragments having a mutation" because the recitation lacks proper antecedent basis in step (A) and because it is unclear which if any fragments have a mutation. It is suggested that Claim 1 be amended to provide proper antecedent basis e.g. at the end of step (A) insert, "thereby hybridizing fragments having a mutation".

d. Claims 1-8 and 19-21 are indefinite in Claim 1 (C) for the recitation "detecting the label" because the recitation lacks proper antecedent basis in step (B) which recites, "labeled protein". It is suggested that Claim 1 be amended to provide proper antecedent basis.

e. Claim 6 is indefinite for the recitation "introducing a label into a nucleic acid" because the recitation lacks proper antecedent basis in Claim 1 which does not recite a step for nucleic acid labeling. It is suggested that the claims be amended to provide proper antecedent basis.

f. Claim 7 is indefinite for the recitation "the label introduced into the nucleic acid" because the recitation lacks proper antecedent basis in Claim 1 which does not recite a step for nucleic acid labeling. It is suggested that the claims be amended to provide proper antecedent basis.

g. Claims 9-18 and 22 are indefinite in Claim 9 because the claim is missing steps (B) and (C).

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h. Claims 9-18 and 22 are indefinite in Claim 9 (A) for the recitation "which fragments are selected from the group consisting of one or more nucleic acid fragments and one or more PNA fragments and have all of a sequence of a full-length gene" because it is unclear how the "fragments" relate to the full length gene. It is unclear whether the "fragments" together, in combination, have "all of a sequence of a full-length gene" or whether each of the fragments have "all of a sequence of a full-length gene". Given the later meaning, it is contradictory that "fragments" can encompass a full-length gene because fragments are inherently incomplete, not full. For purposes of examination, the claim is interpreted as meaning the combination of fragments has all of a sequence of a full-length gene.

i. Claims 9-18 and 22 are indefinite in Claim 9 (B) for the recitation "between the hybridized fragments" because the recitation lacks proper antecedent basis in step (A). It is suggested that Claim 9 be amended to provide proper antecedent basis e.g. at the end of step (A) insert, "thereby hybridizing fragments having a mutation".

j. Claim 21 is indefinite for the recitation "said nucleic acid or PNA" because the recitation lacks proper antecedent basis in Claim 1 which recites "nucleic acid fragments" and "PNA fragments". It is suggested that the claim be amended to provide proper antecedent basis.

k. Claim 22 is indefinite for the recitation "said nucleic acid or PNA" because the recitation lacks proper antecedent basis in Claim 9 which recites "nucleic acid fragments" and "PNA fragments". It is suggested that the claim be amended to provide proper antecedent basis.

l. Claims 28-31 are indefinite in Claim 28 for the recitation "are fixed in a hybridizable condition" because "hybridizable condition" is a relational phrase which requires definition or criteria for determining. It is suggested that Claim 28 be amended to define or recite criteria for determining "hybridizable condition".

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

8. Claims 1- 3, 6-8, 19, 20 and 28-30 are rejected under 35 U.S.C. 102(e) as being anticipated by Chee et al (U.S. Patent No. 5,861,242, filed 9 January 1997).

Regarding Claim 1, Chee et al disclose a method for detecting a nucleic acid fragment having a mutation comprising: hybridizing fragments fixed on a substrate wherein fragments are nucleic acid fragments and have all of a sequence of a full-length gene (HIV reverse transcriptase) with at least one nucleic acid fragment of which a mutation is to be assayed; binding a labeled protein which specifically binds to a mismatched base pair occurring between hybridized fragments having a mutation and identifying a fragment bound by the labeled

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protein by detecting the label thereby detecting a fragment having a mutation (Column 25, line 17-Column 26, line 3).

Regarding Claim 2, Chee et al disclose the method wherein the protein specifically binding to a mismatched base pair is a mismatch binding protein (Column 25, lines 19-24).

Regarding Claim 3, Chee et al disclose the method wherein the mismatch binding protein is Mut S, or analogue thereof (Column 25, lines 19-24).

Regarding Claim 6, Chee et al disclose the method wherein introducing the label and detecting the label are carried out to identify and quantify the fragment having the mutation (Column 25, line 17-Column 26, line 3).

Regarding Claim 7, Chee et al disclose the method wherein the label introduced into the nucleic acid produces a signal different from that produced by the labeled protein and quantification and identification are simultaneously performed (Column 11, line 37-Column 12, line 10 and Column 25, line 17-Column 26, line 3).

Regarding Claim 8, Chee et al disclose the method wherein the nucleic acid to be assayed is labeled with a labeled protein i.e. labeled mismatch protein Column 25, line 17-Column 26, line 3).

Regarding Claim 19, Chee et al disclose the method wherein said fragments are fixed on the substrate only at their 3' end (Column 15, lines 39-57 and Fig. 8-10).

Regarding Claim 20, Chee et al disclose the method wherein said fragments are fixed to the substrate by covalent bonds (Column 15, lines 39-57 and Fig. 8-10).

Regarding Claim 28, Chee et al disclose an article comprising a substrate having a surface on which nucleic acid fragments having all of the sequence of a full-length gene are fixed in a hybridizable condition (Claim 3).

Regarding Claim 29, Chee et al disclose the article wherein said fragments are fixed on the substrate only at their 3' end (Column 15, lines 39-57 and Fig. 8-10).

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Regarding Claim 30, Chee et al disclose the article wherein said fragments are fixed to the substrate by covalent bonds (Column 15, lines 39-57 and Fig. 8-10).

9. Claim 25 is rejected under 35 U.S.C. 102(b) as being anticipated by Fleck et al. (Nucleic Acids Research, 1994, 22(24): 5289-5295).

Regarding Claim 25, Fleck et al disclose a protein specifically bindable to a mismatched base pair wherein said protein is a C/C mismatch binding protein i.e. *Schizosaccharomyces pombe*, *swi4* which specifically binds to c/c mismatched base pairs (page 5291-5292).

Claim Rejections - 35 USC § 102/103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

11. Claims 1-4, 19-21, 28-32 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Wagner et al. (WO 93/02216, published 4 February 1993) as defined by Sambrook et al (Molecular Cloning: A laboratory Manual, Cold Spring Harbor Press, 1989, pages 8.53-8.81).

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Regarding Claim 1, Wagner et al. teach a method for detecting nucleic acid fragment having a mutation comprising: hybridizing at least one nucleic acid fragment, with at least one nucleic acid fragment of which a mutation is to be assayed; binding a labeled substance, said substance specifically binding to a mismatched base pair occurring between the hybridized fragments; and identifying a fragment bound by the labeled substance by detecting the label to thereby detect a nucleic acid having a mutation (page 6, lines 1-25) wherein the at least one fragment is fixed on a substrate (page 7, lines 4-8) and wherein the fragment fixed on the substrate (i.e. hybridization partner) is cDNA (page 13, lines 6-9, Example III and Claim 3) and is prepared by method according to the methods of Sambrook (Example III, page 44, lines 27-31). Sambrook teaches method for preparing cDNA (pages 8.53-8.81) and they specifically and repeatedly teach preparing long cDNAs to thereby create a complete cDNA library (see page 8.54 (3), check size of product; page 8.61(ii), longest cDNA are desired; page 8.64 (5), first strand of cDNA should range in size of 300 bases to 5kb, with majority between 1 and 2 kb; pages 8.70-8.72, a complete section teaching "Size Selection of cDNA"; page 8.76 (2) analysis of cDNAs to obtain cDNA greater than 1kb; and page 8.80-8.81 this section teaches methods of overcoming cDNA synthesis problems e.g. incomplete cDNA).

The preceding rejection is based on judicial precedent following *In re Fitzgerald*, 205 USPQ 594 because Wagner et al. is silent with regard to the hybridization partner having all of a sequence of a full-length gene. However, the sequence of a full-length gene recited in Claim 1 is deemed to be encompassed in the cDNA hybridization partner of Wagner et al. because Wagner's cDNAs are prepared using the method of Sambrook who specifically and repeatedly teach preparation of long cDNA. Alternatively, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the teaching of Sambrook et al to the cDNA preparation of Wagner et al and to analyze the cDNAs prepared and to specifically select and immobilize cDNAs having the full-length sequence as taught by Sambrook for the obvious benefits of analyzing the complete sequence for mutations.

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The burden is on applicant to show that the claimed full-length sequence is either different or non-obvious over that of Wagener et al.

Regarding Claim 2, Wagner et al. disclose the method wherein the substance specifically binding to a mismatched base pair is a mismatch binding protein (page 6, lines 13-17).

Regarding Claim 3, Wagner et al. disclose the method wherein the mismatch binding protein is Mut S (page 6, lines 29-31).

Regarding Claim 4, Wagner et al. disclose the method wherein the substance specifically binding to a mismatched base pair is labeled with at least one kind of substance selected from the group consisting of luminescent proteins, phosphorescent proteins, fluorescent proteins, luminescent substances, fluorescent substances, phosphorescent substances, radioactive substances, stable isotopes, antibodies, antigens enzymes and proteins (page 27, line 22-page 28, line 35).

Regarding Claim 19, Wagner et al. disclose the method wherein the fragments of nucleic acid are bound to the substrate only at their 5' or 3' end i.e. via terminal phosphate groups or hydroxyl terminus (page 19, lines 20-33).

Regarding Claim 20, Wagner et al. disclose the method wherein the fragments of nucleic acid are fixed on the substrate by covalent bonds (page 19, lines 9-10).

Regarding Claim 21, Wagner et al. disclose the method wherein said nucleic acid is cDNA i.e. the immobilized nucleic acid is cDNA (page 6, lines 25-26 and page 13, lines 6-9).

Regarding Claim 28, Wagner et al. disclose an article comprising a substrate having a surface on which nucleic acid fragments having all of a sequence of a full-length gene (page 6, lines 25-28) wherein the fragments are fixed in a hybridizable condition (page 7, lines 4-9) wherein the fragment fixed on the substrate (i.e. hybridization partner) is cDNA (page 13, lines 6-9, Example III and Claim 3) and is prepared by method according to the methods of Sambrook (Example III, page 44, lines 27-31). Sambrook teaches method for preparing cDNA

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(pages 8.53-8.81) and they specifically and repeatedly teach preparing long cDNAs to thereby create a complete cDNA library (see page 8.54 (3), check size of product; page 8.61(ii), longest cDNA are desired; page 8.64 (5), first strand of cDNA should range in size of 300 bases to 5kb, with majority between 1 and 2 kb; pages 8.70-8.72, a complete section teaching "Size Selection of cDNA"; page 8.76 (2) analysis of cDNAs to obtain cDNA greater than 1kb; and page 8.80-8.81 this section teaches methods of overcoming cDNA synthesis problems e.g. incomplete cDNA).

The preceding rejection is based on judicial precedent following *In re Fitzgerald*, 205 USPQ 594 because Wagner et al. is silent with regard to the hybridization partner having all of a sequence of a full-length gene. However, the sequence of a full-length gene recited in Claim 28 is deemed to be encompassed in the cDNA hybridization partner of Wagner et al. because Wagner's cDNAs are prepared using the method of Sambrook who specifically and repeatedly teach preparation of long cDNA for creating a complete cDNA library. Alternatively, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the teaching of Sambrook et al to the cDNA preparation of Wagner et al and to analyze the cDNAs prepared and to specifically select and immobilize cDNAs having the full-length sequence as taught by Sambrook for the obvious benefits of analyzing the complete sequence for mutations.

The burden is on applicant to show that the claimed full-length sequence is either different or non-obvious over that of Wagener et al.

Regarding Claim 29, Wagner et al. disclose the article wherein said fragments are bound to the substrate only at their 5' or 3' end i.e. via terminal phosphate groups or hydroxyl terminus (page 19, lines 20-33).

Regarding Claim 30, Wagner et al. disclose the article wherein said fragments are bound to the substrate by covalent bonds (page 19, lines 9-10).

Regarding Claim 31, Wagner et al. disclose the article wherein said nucleic acid is cDNA (page 13, lines 4-9).

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Regarding (New) Claim 32, Wagner et al. disclose a method for detecting nucleic acid fragment having a mutation comprising: providing at least one polynucleotide fixed on a substrate; a sample comprising at least one nucleic acid fragment of which a mutation is to be assayed; a labeled substance wherein said substance specifically binds to a mismatched base pair resulting from hybridization between a polynucleotide fragment and a fragment comprising a mutation; hybridizing said fragment to said polynucleotide; introducing said labeled substance to specifically bind to any mismatched base pairs; and identifying a fragment bound by the labeled substance to thereby detect a nucleic acid having a mutation (page 6, line 1- page 7, line 8) and wherein the fragment fixed on the substrate (i.e. hybridization partner) is cDNA (page 13, lines 6-9, Example III and Claim 3) and is prepared by method according to the methods of Sambrook (Example III, page 44, lines 27-31). Sambrook teaches method for preparing cDNA (pages 8.53-8.81) and they specifically and repeatedly teach preparing long cDNAs to thereby create a complete cDNA library (see page 8.54 (3), check size of product; page 8.61(ii), longest cDNA are desired; page 8.64 (5), first strand of cDNA should range in size of 300 bases to 5kb, with majority between 1 and 2 kb; pages 8.70-8.72, a complete section teaching "Size Selection of cDNA"; page 8.76 (2) analysis of cDNAs to obtain cDNA greater than 1kb; and page 8.80-8.81 this section teaches methods of overcoming cDNA synthesis problems e.g. incomplete cDNA).

The preceding rejection is based on judicial precedent following *In re Fitzgerald*, 205 USPQ 594 because Wagner et al. is silent with regard to the hybridization partner having all of a sequence of a full-length gene. However, the sequence of a full-length gene recited in Claim 28 is deemed to be encompassed in the cDNA hybridization partner of Wagner et al. because Wagner's cDNAs are prepared using the method of Sambrook who specifically and repeatedly teach preparation of long cDNA for creating a complete cDNA library. Alternatively, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the teaching of Sambrook et al to the cDNA preparation of Wagner et al and to

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analyze the cDNAs prepared and to specifically select and immobilize cDNAs having the full-length sequence as taught by Sambrook for the obvious benefits of analyzing the complete sequence for mutations.

The burden is on applicant to show that the claimed full-length sequence is either different or non-obvious over that of Wagener et al.

Response to Arguments

12. Applicant argues that Wagner et al. do not teach or suggest the use or preparation of a full-length gene or cDNA and that the skilled artisan would not use the method of Wagner et al to prepare a full-length gene or cDNA because the skilled artisan would not have had a reasonable expectation of success. Applicant argues that in contrast to the instantly claimed full-length sequences and cDNAs, Wagner et al uses short oligonucleotides and tiling methods. Applicant further argues that Wagner et al cite Sambrook et al for methods of preparing cDNA, but Sambrook et al does not teach preparing of full-length cDNAs as hybridization partners. Hence, Applicant argues, Wagner et al is not enabling for preparation of full-length cDNAs.

The arguments have been considered but are not found persuasive for numerous reasons. First, as stated above, Wagner et al teach their cDNAs (Example III) are prepared using the method of Sambrook et al (page 44, lines 27-31). And Sambrook specifically and repeatedly teach preparing long cDNAs to thereby create a complete cDNA library (see page 8.54 (3), check size of product; page 8.61(ii), longest cDNA are desired; page 8.64 (5), first strand of cDNA should range in size of 300 bases to 5kb, with majority between 1 and 2 kb; pages 8.70-8.72, a complete section teaching "Size Selection of cDNA"; page 8.76 (2) analysis of cDNAs to obtain cDNA greater than 1kb; and page 8.80-8.81 this section teaches methods of overcoming cDNA synthesis problems e.g. incomplete cDNA). Second, while Wagner et al teach embodiments utilizing oligonucleotides and tiling, they also teach cDNA. Third, Applicant has not provided evidence that Sambrook et al does not teach preparation of full-length cDNA, therefore, Applicant's assertion that Wagner et al using the method of cDNA preparation taught by Sambrook et al is non-enabling is unsubstantiated. As stated above, Sambrook clearly teaches methods of preparing cDNAs.

Claim Rejections - 35 USC § 103

13. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wagner et al. (WO 93/02216, published 4 February 1993) in view of Zoltukhin et al. (U.S. Patent No. 5,874,304, filed 18 January 1996)

Regarding Claim 5, Wagner et al. teach a method for detecting nucleic acid fragment having a mutation comprising: hybridizing at least one nucleic acid fragment, with at least one nucleic acid fragment of which a mutation is to be assayed; binding a labeled substance, said substance specifically binding to a mismatched base pair occurring between the hybridized fragments; and identifying a fragment bound by the labeled substance by detecting the label, thereby detecting a nucleic acid having a mutation (page 6, lines 1-25) wherein at least one fragment is fixed on a substrate (page 7, lines 4-8) and has all of a sequence of a full-length gene (page 6, lines 25-27) and further introducing a label into a nucleic acid fragment to be assayed for mutations (by adding the labeled mismatch-binding protein) and detecting the label to identify the fragment having a mutation (page 6, lines 19-24) but they do not teach the mismatched base pair is labeled with GFP. However, GFP labeled proteins were known in the art at the time the claimed invention was made as taught by Zoltukhin et al. who teaches the advantages of GFP i.e. it does not require cofactors or substrates and it is small in size (Column 1, lines 52-59 and Column 8, lines 22-27). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the GFP label of Zoltukhin et al. to the labeled mismatched base pair binding substance of Wagner et al. for the expected benefit of simplicity by eliminating need for cofactors and substrates as taught by Zoltukhin et al. (Column 1, lines 52-59 and Column 8, lines 22-27).

Response to Arguments

14. Applicant argues that Zoltukhin et al. do not remedy the deficiencies of Wagner et al. and therefore the combination of Wagner et al. and Zoltukhin et al. do not teach or suggest the claimed invention. This argument is not found persuasive for the reasons stated above in ¶ 12.

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15. Claims 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wagner et al. (WO 93/02216, published 4 February 1993) in view of Gifford (U.S. Patent No. 5,750,335, filed 22 April 1993).

Regarding Claim 6, Wagner et al. teach a method for detecting nucleic acid fragment having a mutation comprising: hybridizing at least one nucleic acid fragment, with at least one nucleic acid fragment of which a mutation is to be assayed; binding a labeled substance, said substance specifically binding to a mismatched base pair occurring between the hybridized fragments; and identifying a fragment bound by the labeled substance by detecting the label, thereby detecting a nucleic acid having a mutation (page 6, lines 1-25) wherein at least one fragment is fixed on a substrate (page 7, lines 4-8) and has all of a sequence of a full-length gene (page 6, lines 25-27) and introducing a label into a nucleic acid fragment to be assayed for mutations (by adding the labeled mismatch-binding protein) and detecting the label to identify the fragment having a mutation (page 6, lines 19-24) but they do not teach quantifying the fragment having a mismatched base pair. Gifford teaches a similar method for detecting nucleic acid fragment having a mutation comprising: hybridizing at least one fragment fixed on a substrate with at least one fragment of which mutation is to be assayed (Column 4, lines 10-23 and 66-67) and introducing a label into a fragment to be assayed to identify and quantify the fragment having a mismatch (Column 21, lines 1-10). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the mutation detection of Wagner et al. with the additional quantitation as taught by Gifford et al. for the expected benefit of detecting and quantifying heteroduplex fragments present as taught by Gifford et al. (Column 21, lines 7-10).

Regarding Claim 7, Wagner et al. teach a method for detecting nucleic acid fragment having a mutation wherein the label introduced into the nucleic acid fragment to be assayed

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for mutations (by adding the labeled mismatch-binding protein) and detecting the label of the are carried out in order to identify the fragment having a mutation (page 6, lines 19-24) but they do not teach the a label different from the label attached to the mismatch binding substance. Gifford et al. teach the similar method wherein the label introduced into the nucleic acid to be assayed for mutations produces a signal different from that produce by the label attached to the substance specifically binding to a mismatched base pair wherein quantification and identification of the fragment are performed simultaneously i.e. compare to identify and quantify (Column 21, lines 1-18).

Regarding Claim 8, Wagner et al. teach the method wherein the fragment to be assayed is labeled by being bound to a labeled substance which specifically binds to a mismatched base pair wherein the substance is labeled with at least one kind of substance selected from the group consisting of luminescent proteins, phosphorescent proteins, fluorescent proteins, luminescent substances, fluorescent substances, phosphorescent substances, radioactive substances, stable isotopes, antibodies, antigens enzymes and proteins (page 27, lines 22-32) but they do not teach the nucleic acid fragments are labeled. Gifford et al. teach the similar method wherein the nucleic acid fragments to be assayed are labeled with at least on kind of label selected from the group consisting of luminescent substances, fluorescent substances, phosphorescent substances, stable isotopes, radioactive substances (Column 10, lines 33-41). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the labeling taught by Wagner et al. with the additional label on the nucleic acid to be assayed as taught by Gifford et al. for the expected benefit of quantifying the heteroduplexes in a sample as taught by Gifford et al. (Column 21, lines 3-6).

Response to Arguments

16. Applicant argues that Gifford et al. do not remedy the deficiencies of Wagner et al. and therefore the combination of Wagner et al. and Gifford et al. do not teach or suggest the claimed invention. This argument is not found persuasive for the reasons stated above in ¶ 12.

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17. Claims 9-18, 22 & 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wagner et al. (WO 93/02216, published 4 February 1993) in view of Chirikjian et al. (U.S. Patent No. 5,763,178, filed 7 June 1996) and Goldrick (U.S. Patent No. 5,891,629, filed 28 September 1995).

Regarding Claim 9, Wagner et al. teach a method for detecting nucleic acid fragment having a mutation comprising: hybridizing at least one nucleic acid fragment, with at least one nucleic acid fragment of which a mutation is to be assayed; binding a labeled substance, said substance specifically binding to a mismatched base pair occurring between the hybridized fragments; and identifying a fragment bound by the labeled substance by detecting the label, thereby detecting a nucleic acid having a mutation (page 6, lines 1-25) wherein at least one fragment is fixed on a substrate (page 7, lines 4-8) and wherein the fragment fixed on the substrate (i.e. hybridization partner) is DNA prepared from any of source using any known technique e.g. naturally occurring DNA (page 16, lines 21-25). Wagner et al. do not teach the method wherein a substance which recognizes the mismatched base pair cleaves the hybridized fragments and labeling the remaining fragments. However, Chirikjian et al. teach a similar method for detecting a nucleic acid fragment having a mutation comprising: hybridizing nucleic acid fragments with nucleic acid fragments of which a mutation is to be assayed treating a mismatched base pair occurring between the fragments with a substance specifically recognizing and cleaving the mismatched base pair labeling the cleaved fragments (Column 9, lines 33-38) and identifying the labeled fragment to thereby detect a nucleic acid having a mutation (Column 3, lines 8-28). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the mismatch binding protein of Wagner et al. with the mismatch binding protein which cleaves as taught by Chirikjian et al. for the expected benefit of eliminating the necessity of PCR amplification which introduces spurious point mutations and to thereby detect, identify and localize a nucleic acid having a point

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mutation accurately, economically and efficiently as taught by Chirikjian et al. (Column 6, lines 40-45).

Regarding Claim 10, Wagner et al. teach the method wherein said fragment is fixed on the substrate at the 5' end (page 19, lines 20-25) but they do not teach the 3' end of the fragment is blocked and the labeling of the fragment is performed by 3' end addition. However, Chirikjian et al. teach the similar method wherein the labeling of the cleaved fragment is by a 3' end addition reaction. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the labeling reaction of Wagner et al. with the 3' addition reaction of Chirikjian et al. based on mutation being detected for the expected benefit of detecting a point mutation accurately, economically and efficiently as taught by Chirikjian et al. (Column 6, lines 40-45).

Regarding Claim 11, Wagner et al. teach the method wherein the binding substance is Mut S (page 6, lines 29-31) but they do not teach the binding substance is a nuclease. However, Chirikjian et al. teach the similar method wherein the binding substance is a nuclease (Column 7, lines 1-19). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the Mut S binding substance of Wagner et al. with the nuclease as taught by Chirikjian et al. based on mutation being detected for the expected benefit of detecting a point mutation accurately, economically and efficiently as taught by Chirikjian et al. (Column 6, lines 40-45).

Regarding Claim 12, Chirikjian et al. teach the similar method wherein the mismatch binding substance is a nuclease comprising numerous nuclease enzymes known in the art (Column 7, lines 1-25) but they do not specifically teach the nuclease is S1 nuclease, Mung bean nuclease or RNase H. However, Goldrick teach a similar method for detecting a mutation comprising: hybridizing a nucleic acid fragment with a fragment to be assayed; treating a mismatched base pair with a substance specifically recognizing and cleaving the mismatch base pair to cleave; and identifying the cleaved fragment to identify the mutated fragment

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wherein the cleaving substance is selected from S1 nuclease and Mung bean nuclease (Column 15, lines 2744). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the mismatch-bind substance of Wagner et al. and Chirikjian et al. with functionally equivalent nuclease i.e. S1 nuclease and/or Mung bean nuclease taught by Goldrick based on available reagents, mutation of interest and desired results to optimize experimental conditions to thereby maximize experimental results. The courts have further stated with regard to chemical homologs that the greater the physical and chemical similarities between the claimed species and any species disclosed in the prior art, the greater the expectation that the claimed subject matter will function in an equivalent manner (see *Dillon*, 99 F.2d at 696, 16 USPQ2d at 1904).

Regarding Claim 13, Chirikjian et al. teach the similar method wherein the labeling is performed by an enzyme reaction utilizing a label i.e. a glycosylase-associated label (Column 9, lines 33-37).

Regarding Claim 14, Chirikjian et al. teach the similar method wherein the reaction is 3' addition (Column 9, lines 33-37).

Regarding Claim 15, Chirikjian et al. teach the similar method wherein the fragment is labeled with a fluorescent substance (Column 9, lines 35-37).

Regarding Claim 16, Chirikjian et al. teach the similar method wherein introducing a label into the fragment to be assayed are carried out in order to detect and quantify the fragment having a mismatched base (Column 9, lines 58-65).

Regarding Claim 17, Chirikjian et al. teach the similar method wherein quantification and identification of the fragment are simultaneously performed (Column 9, lines 39-52).

Regarding Claim 18, Chirikjian et al. teach the similar method wherein the fragment is labeled with a fluorescent substance (Column 9, lines 35-37).

Regarding Claim 22, Wagner et al. teach the method wherein the nucleic acid is cDNA (page 13, lines 4-9).

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Regarding (New) Claim 33, Wagner et al. teach a method for detecting nucleic acid fragment having a mutation comprising: providing at least one polynucleotide fixed on a substrate; and a sample comprising at least one nucleic acid fragment; hybridizing said fragment to said polynucleotide; treating a mismatched base pair occurring between said hybridized fragment and polynucleotide with a substance that specifically recognizes the mismatch; labeling the fragment; and identifying the labeled fragment to thereby detect a nucleic acid having a mutation (page 6, line 1-page 7, line 8) and wherein the fragments have all of a sequence of a full-length gene (page 6, lines 25-27). Wagner et al. do not teach the method wherein a substance which recognizes the mismatched base pair cleaves the hybridized fragments and labeling the remaining fragments. However, Chirikjian et al. teach a similar method for detecting a nucleic acid fragment having a mutation comprising: hybridizing nucleic acid fragments with nucleic acid fragments of which a mutation is to be assayed treating a mismatched base pair occurring between the fragments with a substance specifically recognizing and cleaving the mismatched base pair labeling the cleaved fragments (Column 9, lines 33-38) and identifying the labeled fragment to thereby detect a nucleic acid having a mutation (Column 3, lines 8-28). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the mismatch binding protein of Wagner et al. with the mismatch binding protein which cleaves as taught by Chirikjian et al. for the expected benefit of eliminating the necessity of PCR amplification which introduces spurious point mutations and to thereby detect, identify and localize a nucleic acid having a point mutation accurately, economically and efficiently as taught by Chirikjian et al. (Column 6, lines 40-45).

Response to Arguments

18. Applicant argues that Chirikjian et al. and Goldrick do not remedy the deficiencies of Wagner et al. and therefore the combination of Wagner et al., Chirikjian et al. and Goldrick et al. do not teach or suggest the claimed invention. This argument is not found persuasive for the reasons stated above in ¶ 12.

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19. Claims 23-25 & 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wagner et al. (WO 93/02216, published 4 February 1993) in view of Zoltukhin et al. (U.S. Patent No. 5,874,304, filed 18 January 1996) and Fleck et al. (Nucleic Acids Research, 1994, 22(24): 5289-5295).

Regarding Claim 23, Wagner et al. teach a substance specifically bindable to a mismatched base pair wherein said substance is labeled (page 7, lines 10-16) but they do not teach the label is GFP. However, GFP labeled proteins were known in the art at the time the claimed invention was made as taught by Zoltukhin et al. who teaches the advantages of GFP i.e. it does not require cofactors or substrates and it is small in size (Column 1, lines 52-59 and Column 8, lines 22-27). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the GFP label of Zoltukhin et al. to the labeled mismatched base pair binding substance of Wagner et al. for the advantages of GFP taught by Zoltukhin et al. i.e. GFP is small in size and does not require cofactors or substrates (Column 1, lines 52-59 and Column 8, lines 22-27).

Regarding Claim 24, Wagner et al. teach a substance specifically bindable to a mismatched base pair wherein said substance is labeled wherein the substance is the MutS protein or a functional derivative thereof (page 6, lines 19-31) but they do not teach the mismatch binding protein binds a c/c mismatch. However, c/c mismatch binding proteins were well known in the art at the time the claimed invention was made as taught by Fleck et al. who teach the MutS homologue of *Schizosaccharomyces pombe*, *swi4* which specifically binds to c/c mismatched base pairs (page 5292). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify mismatch binding protein, mutS of Wagner et al. with the mutS homologue taught by Fleck et al. for the expected benefit of base-specific mismatch binding as taught by Fleck et al. (page 5294, last paragraph).

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Regarding Claim 25, Wagner et al. teach a substance specifically bindable to a mismatched base pair wherein said substance is labeled wherein the substance is the MutS protein or a functional derivative thereof (page 6, lines 19-31) but they do not teach the mismatch binding protein binds a c/c mismatch. However, c/c mismatch binding proteins were well known in the art at the time the claimed invention was made as taught by Fleck et al. who teach the MutS homologue of *Schizosaccharomyces pombe*, swi4 which specifically binds to c/c mismatched base pairs (page 5292). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify mutS mismatch binding protein taught by Wagner et al. with the mutS homologue of Fleck et al. for the expected benefit of base-specific mismatch binding as taught by Fleck et al. (page 5294, last paragraph).

Regarding Claim 27, Wagner et al. the substance specifically binding to a mismatched base pair is labeled with at least one kind of substance selected from the group consisting of luminescent proteins, phosphorescent proteins, fluorescent proteins, luminescent substances, fluorescent substances, phosphorescent substances, radioactive substances, stable isotopes, antibodies, antigens enzymes and proteins (page 27, lines 22-32).

Response to Arguments

20. Applicant argues that Zoltukhin et al. and Fleck et al. do not remedy the deficiencies of Wagner et al. and therefore the combination of Wagner et al, Zoltukhin et al. and Fleck et al. do not teach or suggest the claimed invention. This argument is not found persuasive for the reasons stated above in ¶ 12.

21. Claims 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chee et al (U.S. Patent No. 5,861,242, filed 9 January 1997) in view of Zoltukhin et al. (U.S. Patent No. 5,874,304, filed 18 January 1996)

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Regarding Claims 4 and 5, Chee et al teach a method for detecting a nucleic acid fragment having a mutation comprising: hybridizing fragments fixed on a substrate wherein fragments are nucleic acid fragments and have all of a sequence of a full-length gene (HIV reverse transcriptase) with at least one nucleic acid fragment of which a mutation is to be assayed; binding a labeled protein which specifically binds to a mismatched base pair occurring between hybridized fragments having a mutation and identifying a fragment bound by the labeled protein by detecting the label thereby detecting a fragment having a mutation (Column 25, line 17-Column 26, line 3) wherein the mismatch protein is indirectly labeled (Column 25, lines 24-27) but they do not teach the mismatched base pair is labeled a fluorescent protein (Claim 4) e.g. GFP (Claim 5). However, GFP labeled proteins were known in the art at the time the claimed invention was made as taught by Zoltukhin et al. who teaches the advantages of GFP i.e. it does not require cofactors or substrates and it is small in size (Column 1, lines 52-59 and Column 8, lines 22-27). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the GFP label of Zoltukhin et al. to the labeled mismatched base pair binding substance of Chee et al. for the expected benefit of simplicity by eliminating need for cofactors and substrates as taught by Zoltukhin et al. (Column 1, lines 52-59 and Column 8, lines 22-27).

22. Claims 9-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chee et al (U.S. Patent No. 5,861,242, filed 9 January 1997) in view of Chirikjian et al. (U.S. Patent No. 5,763,178, filed 7 June 1996) and Goldrick (U.S. Patent No. 5,891,629, filed 28 September 1995).

Regarding Claim 9, Chee et al teach a method for detecting a nucleic acid fragment having a mutation comprising: hybridizing fragments fixed on a substrate wherein fragments are nucleic acid fragments and have all of a sequence of a full-length gene (HIV reverse transcriptase) with at least one nucleic acid fragment of which a mutation is to be assayed; binding a labeled protein which specifically binds to a mismatched base pair occurring between hybridized fragments having a mutation and identifying a fragment bound by the labeled protein by detecting the label thereby detecting a fragment having a mutation (Column 25, line 17-Column 26, line 3) wherein the mismatch protein is indirectly labeled (Column 25, lines 24-27) but they do not teach the method wherein a substance which recognizes the mismatched base pair cleaves the hybridized fragments and labeling the remaining fragments. However, Chirikjian et al. teach a similar method for detecting a nucleic acid fragment having a mutation comprising: hybridizing nucleic acid fragments with nucleic acid fragments of which a mutation is to be assayed treating a mismatched base pair occurring between the fragments with a substance specifically recognizing and cleaving the mismatched base pair labeling the cleaved fragments (Column 9, lines 33-38) and identifying the labeled fragment to thereby detect a nucleic acid having a mutation (Column 3, lines 8-28). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the mismatch binding protein of Chee et al. with the mismatch binding protein which cleaves as taught by Chirikjian et al. for the expected benefit of eliminating the necessity of PCR amplification which introduces spurious point mutations and to thereby detect, identify and localize a nucleic acid having a point mutation accurately, economically and efficiently as taught by Chirikjian et al. (Column 6, lines 40-45).

Regarding Claim 10, Chee et al. teach the method wherein said fragment is fixed on the substrate at the 5' end (Column 15, lines 39-57) but they do not teach the 3' end of the fragment is blocked and the labeling of the fragment is performed by 3' end addition. However, Chirikjian et al. teach the similar method wherein the labeling of the cleaved fragment is by a 3'

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end addition reaction. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the labeling reaction of Chee et al. with the 3' addition reaction of Chirikjian et al. based on mutation being detected for the expected benefit of detecting a point mutation accurately, economically and efficiently as taught by Chirikjian et al. (Column 6, lines 40-45).

Regarding Claim 11, Chee et al. teach the method wherein the binding substance is MutS (Column 25, lines 1-24) but they do not teach the binding substance is a nuclease. However, Chirikjian et al. teach the similar method wherein the binding substance is a nuclease (Column 7, lines 1-19). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the MutS binding substance of Chee et al. with the nuclease as taught by Chirikjian et al. based on mutation being detected for the expected benefit of detecting a point mutation accurately, economically and efficiently as taught by Chirikjian et al. (Column 6, lines 40-45).

Regarding Claim 12, Chirikjian et al. teach the similar method wherein the mismatch binding substance is a nuclease comprising numerous nuclease enzymes known in the art (Column 7, lines 1-25) but they do not specifically teach the nuclease is S1 nuclease, Mung bean nuclease or RNase H. However, Goldrick teach a similar method for detecting a mutation comprising: hybridizing a nucleic acid fragment with a fragment to be assayed; treating a mismatched base pair with a substance specifically recognizing and cleaving the mismatch base pair to cleave; and identifying the cleaved fragment to identify the mutated fragment wherein the cleaving substance is selected from S1 nuclease and Mung bean nuclease (Column 15, lines 2744). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the mismatch-bind substance of Chee et al. and Chirikjian et al. with functionally equivalent nuclease i.e. S1 nuclease and/or Mung bean nuclease taught by Goldrick based on available reagents, mutation of interest and desired results to optimize experimental conditions to thereby maximize experimental results. The

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courts have further stated with regard to chemical homologs that the greater the physical and chemical similarities between the claimed species and any species disclosed in the prior art, the greater the expectation that the claimed subject matter will function in an equivalent manner (see *Dillon*, 99 F.2d at 696, 16 USPQ2d at 1904).

Regarding Claim 13, Chirikjian et al. teach the similar method wherein the labeling is performed by an enzyme reaction utilizing a label i.e. a glycosylase-associated label (Column 9, lines 33-37).

Regarding Claim 14, Chirikjian et al. teach the similar method wherein the reaction is 3' addition (Column 9, lines 33-37).

Regarding Claim 15, Chirikjian et al. teach the similar method wherein the fragment is labeled with a fluorescent substance (Column 9, lines 35-37).

Regarding Claim 16, Chirikjian et al. teach the similar method wherein introducing a label into the fragment to be assayed are carried out in order to detect and quantify the fragment having a mismatched base (Column 9, lines 58-65).

Regarding Claim 17, Chirikjian et al. teach the similar method wherein quantification and identification of the fragment are simultaneously performed (Column 9, lines 39-52).

Regarding Claim 18, Chirikjian et al. teach the similar method wherein the fragment is labeled with a fluorescent substance (Column 9, lines 35-37).

23. Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chee et al (U.S. Patent No. 5,861,242, filed 9 January 1997) in view of Zoltukhin et al. (U.S. Patent No. 5,874,304, filed 18 January 1996)

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Regarding Claim 23, Chee et al teach a labeled mismatch protein (Column 25, lines 19-27) but they are silent regarding the label. However, labeled proteins were well known in the art at the time the claimed invention was made as taught by Zoltukhin et al. who teaches the advantages of GFP-labeled proteins i.e. the label does not require cofactors or substrates and it is small in size (Column 1, lines 52-59 and Column 8, lines 22-27). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the GFP label of Zoltukhin et al. to the labeled mismatched binding protein of Chee et al. for the advantages of GFP taught by Zoltukhin et al. i.e. GFP is small in size and does not require cofactors or substrates (Column 1, lines 52-59 and Column 8, lines 22-27).

24. Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chee et al (U.S. Patent No. 5,861,242, filed 9 January 1997) in view of Zoltukhin et al. (U.S. Patent No. 5,874,304, filed 18 January 1996) as applied to Claim 23 above and further in view of Fleck et al. (Nucleic Acids Research, 1994, 22(24): 5289-5295).

Regarding Claim 24, Chee et al teach a labeled mismatch protein e.g. Mut S and equivalents (Column 25, lines 19-27) and Zoltukhin et al teach a motivation for labeling the mismatch protein with DFP, but Chee and Zoltukhin do not teach the mismatch binding protein binds a c/c mismatch. However, c/c mismatch binding proteins were well known in the art at the time the claimed invention was made as taught by Fleck et al. who teach the MutS homologue of *Schizosaccharomyces pombe*, *swi4* which specifically binds to c/c mismatched base pairs (page 5292). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify mismatch binding protein, mutS of

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Chee et al. with the mutS equivalent as taught by Fleck et al. for the expected benefit of base-specific mismatch binding as taught by Fleck et al. (page 5294, last paragraph).

25. Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chee et al (U.S. Patent No. 5,861,242, filed 9 January 1997) and Fleck et al. (Nucleic Acids Research, 1994, 22(24): 5289-5295).

Regarding Claim 25, Chee et al teach a labeled mismatch protein e.g. Mut S and equivalents (Column 25, lines 19-27) but they do not specifically teach a mismatch binding protein equivalent is a C/C mismatch binding protein. However, C/C mismatch binding proteins were well known in the art at the time the claimed invention was made as taught by Fleck et al who teach *Schizosaccharomyces pombe*, *swi4* (page 5291-5292) wherein, *swi4* is a MutS homologue (Abstract). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the *swi4* C/C mismatch binding protein of Fleck et al to the Mut S homologues of Chee et al for the obvious benefits of global mismatch detection.

26. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fleck et al. (Nucleic Acids Research, 1994, 22(24): 5289-5295) and Chee et al (U.S. Patent No. 5,861,242, filed 9 January 1997) in view of Zoltukhin et al. (U.S. Patent No. 5,874,304, filed 18 January 1996).

Regarding Claim 27, Fleck et al. teach a protein which specifically binds to c/c mismatched base pair i.e. *Schizosaccharomyces pombe*, *swi4* (page 5291-5292) wherein, *swi4*

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is a MutS homologue (Abstract) but they do not teach *swi4* is labeled with a protein. However, Chee et al teach labeled mismatch proteins e.g. Mut S and its equivalents (Column 25, lines 19-27) and Zoltukhin et al teach a motivation for labeling the mismatch protein with a fluorescent protein i.e. the label does not require cofactors or substrates and it is small in size (Column 1, lines 52-59 and Column 8, lines 22-27). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the label of Zoltukhin et al. to the labeled mismatched binding protein of Fleck et al for the advantages taught by Zoltukhin et al. i.e. GFP is small in size and does not require cofactors or substrates (Column 1, lines 52-59 and Column 8, lines 22-27).

Response to Declaration

27. The declaration filed on 30 July 2001 under 37 CFR 1.131 is sufficient to overcome the Wagner et al. reference.

Dr. Yasushi argues that Wagner et al. do not teach or suggest the use of a DNA with the sequence of a full-length gene as a hybridization partner. Dr. Yasushi states that it is his understanding of Wagner et al. that the hybridization partner is an EST or shotgun fragments and that the standard methods referred to in Example III of Wagner et al. do not include preparation of full-length cDNAs or full-length genes. These arguments are not found persuasive because as stated above, Wagner et al. specifically teach their hybridization partner is cDNA prepared using the methods of Sambrook et al who specifically teach methods for preparing cDNAs of desired length to thereby construct a complete cDNA library (page 8.53-8.01).

Dr. Yasushi also argues that the "tiling method" of Wagner et al. require a high number of overlapping fragments each fixed on a support in contrast to the claimed invention which requires only one full-length DNA. This argument is not found persuasive because while

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Wagner et al. teach an embodiment comprising tiling, they also and specifically the cDNA (Example III).

Conclusion

28. No claim is allowed.
29. The examiner's Art Unit has changed from 1655 to 1634. Please address future correspondence to Art Unit 1634.
30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:30 TO 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



BJ Forman, Ph.D.
Patent Examiner
Art Unit: 1634
August 19, 2002



W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600